Precision Medicine/Health

366

Predicting survival in patients with neuroendocrine prostate cancer*

Anthony Tabiim[1], Jabra Zarka[2], Joanina K. Gicobi[2], Peter Rosen[2], Nicole Becker[2], Miguel Muniz[2], Daniel S. Childs[2], Lewis R. Roberts[3] and Jacob J. Orme[2]
[1]Mayo Clinic Graduate School of Biomedical Sciences; [2]Department of Medical Oncology, Mayo Clinic, Rochester USA and [3]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester USA

OBJECTIVES/GOALS: The impact of genetic alterations on survival in patients with neuroendocrine prostate cancer (NEPC) is unclear. This study assessed how genetic alterations and tumor mutational burden (TMB) affect overall survival (OS) in patients with NEPC treated at Mayo Clinic. METHODS/STUDY POPULATION: Demographic, clinicopathologic, and genomic data from patients with NEPC treated at Mayo Clinic (2015–2025) were abstracted from electronic medical records. Patients had consented to research and received at least one cycle of therapy. Descriptive statistics summarized patient characteristics, and survival was estimated with Kaplan–Meier analysis. OS was compared by disease type (de novo vs treatment-emergent NEPC), TMB (high vs low), and RB1, TP53, and PTEN alteration status. RESULTS/ANTICIPATED RESULTS: Among 66 patients in the study, the average age at NEPC diagnosis was 67.5 years. There were no significant differences between the age at diagnosis of de novo and treatment emergent NEPC (t-NEPC). t-NEPC made up 77.3% of the cohort. Median follow-up was 46.5 months (IQR 28–120). The most common alteration was TP53. RB1 alterations were associated with significantly shorter OS compared to patients without RB1 alterations (mOS Not Reached (NR) vs 13.8 months; p = 0.0056). Similarly, patients with high TMB had worse overall survival (mOS NR vs 14.9 months; p = 0.077). We did not observe worse OS in patients with alterations in TP53 or PTEN. RB1 alteration and high TMB were the strongest predictors of worse survival. DISCUSSION/SIGNIFICANCE OF IMPACT: RB1 alterations and high TMB predict poor survival in patients with NEPC, highlighting potential biomarkers for risk stratification. TP53 and PTEN did not significantly affect OS. Early genomic profiling and targeted management of actionable alterations such as BRCA and ATM may improve survival and inform future translational studies.

367

High-risk peripheral blood immune dysregulation signature is elevated in obesity and is reduced by lifestyle interventions

Anthony Andrew Moore, Ananthakrishnan Ganesan, Jeanna Enriquez, Hong Zheng, Purvesh Khatri
Stanford University School of Medicine

OBJECTIVES/GOALS: The Human Immune Dysregulation Evaluation Framework (Hi-DEF) quantifies myeloid dysregulation in infectious and non-infectious illness using peripheral blood gene expression (Moore, Nat Med). We evaluated immune dysregulation in obesity and quantified the changes in dysregulation due to lifestyle and medical interventions. METHODS/STUDY POPULATION: We assessed the association of obesity with myeloid dysregulation in the Framingham Cohort using linear regression. In two additional datasets (GSE66175, GSE19790), we assessed the effect of dietary interventions and bariatric surgery on myeloid dysregulation using paired Wilcoxon rank sum test pre- and post- intervention and Pearson's correlation. RESULTS/ANTICIPATED RESULTS: In the Framingham cohort (n=5321), myeloid dysregulation score was associated with BMI (p=2.2e-6) after correcting for age and sex. Patients assigned to diet/exercise experienced significant reductions in myeloid score after 3 months (n=63, p=1.2e-7), which was not seen in controls (n=63, p=0.29). Change in myeloid score was significantly correlated with change in weight loss (r=0.32, p=0.006). This reduction in myeloid dysregulation was also seen post-bariatric surgery (n=11, p=0.0001). DISCUSSION/SIGNIFICANCE OF IMPACT: Patients with obesity have significantly higher myeloid dysregulation compared to healthy subjects, which is modifiable with lifestyle and medical interventions. These results suggest that we may be able to quantify and monitor immune dysregulation from obesity which may place these patients at risk for worse outcomes.

369

Serum bile acid and gut microbiome composition in heterogeneous individuals

Lauren Gonsalves[1], Hillary Schiff[1], Bharathi Laxman[1], Sarbani Adhikari[1], Andrew Craver[2], Brisa Aschebrook-Kilfoy[1], Ran Blekhman[1] and Sonia Kupfer[1]
[1]University of Chicago and [2]University of Chicago DFI Host-Microbe Metabolomics and Microbiome Metagenomics Facilities

OBJECTIVES/GOALS: Colorectal cancer risk varies across populations. Bile acid (BA) composition and the gut microbiome can impact CRC risk, but their differences across populations is poorly understood. We characterized serum BA and gut microbiome profiles in non-Hispanic Black and White Americans and examined associations with diet and social determinants of health. METHODS/STUDY POPULATION: To characterize BA composition, participants from the Chicago Multiethnic Prevention and Surveillance Study with a banked serum sample (n=100) were selected, with a subset of participants having completed a diet recall survey (ASA24; n=23). Sixty-two BA (primary, secondary, and glyco/tauro-conjugated BA) from serum samples were analyzed using liquid chromatography-mass spectrometry. For microbiome profiling, normal colonic biopsy samples from non-cancer participants were obtained from the Digestive Disease Research Core Center's Integrative Clinical and Biospecimens Core (University of Chicago; n=109). Following DNA extraction, the mucosally adherent microbial community was assessed by 16S rRNA sequencing. RESULTS/ANTICIPATED RESULTS: Of the BA detected in over 80% of the samples, glycochenodeoxycholic acid (GCDCA) and

deoxycholic (DCA) had the highest median concentrations (56.7 and 55.0 μg/mL, respectively). Moderate positive correlations between DCA/isoDCA and calories, fat, and cholesterol were observed. The linear regression model employed to understand the relationship between log-transformed DCA and race, age, sex, and area deprivation index highlighted age as a key predictor of DCA level when controlling for other covariates. Microbiome analysis revealed that diversity was not different when comparing sexes, races, or colonic anatomic locations. At the phylum level, taxa belonging to the Bacillota and Bacteroidota phyla were common across samples. DISCUSSION/SIGNIFICANCE OF IMPACT: These data and subsequent analysis, including additional BA analysis, improvement of the regression model, and deeper analysis of microbiome community related to BA metabolism, will provide additional context to the role of social and biological factors in better understanding differences in CRC risk and pathogenesis across human populations.

370

Mechanism of agmatine prodrugs for alleviating chronic pain and opioid addiction*

Lukas Caye, Cristina D. Peterson, Cecilia Barajas, Kelley F. Kitto, Parker Jones, G.L. Wilcox and C.A. Fairbanks
University of Minnesota

OBJECTIVES/GOALS: There remains an urgent need for the development of safe and effective therapeutics for the long-term management of pain. We evaluated our novel analgesic in multiple preclinical models to assess its abuse liability, analgesic efficacy in models of chronic pain, and its mechanism of action in *ex vivo* spinal cord slices. METHODS/STUDY POPULATION: We evaluated SSA3's abuse liability by utilizing an IV self-administration paradigm. In this experiment, rats are placed in a chamber and have the option to press a drug-infusion lever or a control lever. Abuse liability was determined based on extent of lever pressing on the drug-infusion lever. To evaluate chronic pain efficacy, mice underwent a spared nerve injury (SNI) which induces sustained hypersensitivity in their hind paw. Mice were then treated with SSA3, and their hypersensitivity was assessed. Finally, the mechanism of action was investigated through patch clamp electrophysiology recordings taken from excised spinal cord slices in mice. We recorded currents from neurons involved in the pain signaling pathway before and after application of our compound to observe drug efficacy at the cellular level. RESULTS/ANTICIPATED RESULTS: Our results demonstrated that in a pre-clinical IV self-administration paradigm, SSA3 exhibited no abuse liability, indicated by a lack of drug intake or escalation of drug intake. Results from our SNI model of chronic pain reveal that when SSA3 is administered directly onto the spinal cord via intrathecal injection, it is efficacious in reversing the pain hypersensitivity established by the model, suggesting a spinally mediated mechanism of action. Finally, we observed that SSA3 effectively reduced the amplitude of NMDA receptor-mediated excitatory postsynaptic currents in a concentration-dependent manner. This reduction in amplitude suggests our compound's analgesic efficacy comes from the inhibition of spinally mediated NMDA receptor signaling. DISCUSSION/SIGNIFICANCE OF IMPACT: This investigation into the therapeutic potential of substituted agmatine for the management of chronic pain revealed several key insights. Our drug is efficacious in models of chronic pain and, importantly, lacks the abuse liability commonly seen with analgesic drugs. Our drug's mechanism of action involves inhibition of spinal NMDA receptors.

372

Cognitive impairment is associated with increased nightly heart rate variability in a large longitudinal study of sleep in cirrhosis

Adam Buckholz[1], Avesh Thuluvath[2], Himel Mallick[3] and Olivia Blocker[4]
[1]Weill Cornell Medicine; [2]Columbia University Medical Center; [3]Weill Cornell Department of Population Health Sciences and [4]Weill Cornell Medical Center Division of Gastroenterology and Hepatology

OBJECTIVES/GOALS: Heart rate variability (HRV) is the variation in time between each heartbeat and an important biomarker of autonomic nervous system function, with higher HRV generally associated with improved parasympathetic tone and cardiac health. The most reliable measurement is during sleep, but sleep and HRV are both understudied in cirrhosis and HE. METHODS/STUDY POPULATION: We longitudinally assessed sleep and resting cardiovascular biomarkers in a cohort (n=119) of patients with cirrhosis using Oura, a commercially available fitness tracker. Baseline clinical data, psychometric hepatic encephalopathy score (PHES) and 6 months of passive sleep data collection were obtained. 117 participants enrolled, 6 collected no sleep data, 13 did not complete PHES; 10,065 nights (n=98) were available, and 9,692 were analyzed after outlier trimming (top and bottom 1% of data). Mixed effects modeling (MEM) assessed associations. Pre-specified covariates included age, gender, sodium, albumin, bilirubin, INR, and ascites. Missing data was not imputed. RESULTS/ANTICIPATED RESULTS: In univariable analysis, impaired cognition by PHES was associated with increased average HRV (B 5.2 95%CI 0.25, 10.1 p=0.04) but not respiratory rate, heart rate, or lowest measured heart rate. CTP Score (B -1.8 95%CI -3.0, -0.6 p<0.01) and INR (B -6.1 95%CI -11.6, -0.5 p=0.03) were inversely associated with HRV. Higher baseline albumin (B 3.9 95%CI 0.34, 7.4 p=0.03) and sodium (B 1.0 95%CI 0.18, 1.75 p=0.02) were associated with increased HRV, while age, gender, and creatinine did not significantly associate with HRV. In a MEM adjusting for the pre-specified covariates, the association was greater (B 8.85 95%CI 3.85, 13.9 p<0.01), remaining significant after log-normalizing HRV. In a sensitivity analysis adjusting for current alcohol use or prior variceal bleed, the results